REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-3 and 5-8 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-3 and 5-8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Musacchio et al. (1996) in view of Li et al. (WO98/14467) and Proudfoot et al. (WO02/28419). The examiner states that:

> The prior art teaches that proteins expressed as inclusion bodies in *E. coli* after solubilization can be purified using reverse phase chromatography (see Musacchio et al. and Li et al.). Interposing a reverse Phase Chromatography is taught by Musacchio… the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose.

This rejection is respectfully traversed.

Regarding the first part of the examiner's statement above, it should be pointed out that the secondary Li reference teaches at page 12, lines 4-6 that:

> The recovered, solubilized protein may then be purified using conventional techniques. Optionally, if deemed necessary, the target

> protein may be refolded prior to purification. (emphasis added)

It is clear from Li's disclosures and teachings that purification steps, such as reverse phase chromatography, would be done immediately after solubilization only if there is no need for refolding. See page 15, lines 1-2, where Li teaches that:

> After solubilization and, optionally, refolding of target proteins, these proteins can be recovered and purified by methods well known in the art.

One of ordinary skill in the art can only interpret this as teaching the order of steps to be either 1) solubilization and 2) purification with no need for refolding necessary or 1) solubilization, 2) refolding and 3) purification. In any event, there is no teaching in Li that would suggest a purification step, such as reverse phase chromatograph (RPC), after solubilization but before the refolding/renaturation step, as is presently claimed. This order of steps is further confirmed by the process for purifying chemokines from bacterial inclusion bodies that is disclosed at pages 24-28 of the Li reference. Clearly, reading Li, one of ordinary skill in the art would be taught to purify chemokine only after a refolding step, if the refolding step is warranted.

Turning to Musacchio as the primary reference, it should be pointed out here that Musacchio's teaching is a bit

unusual in that purification via RPC was the only purification process leading to success, i.e., the recovery of pure correctly refolded Opc protein. See page 755, first paragraph of left column, where it is taught that "other purification procedures were used without success". While Musacchio discloses interposing a RPC step between the solubilization step and the refolding step for the purification of Opc protein, Musacchio also teaches that the order of the refolding and purification steps is not important. Page 757, second full paragraph in the left column, teaches that, in preliminary experiments, protein renaturation carried out prior to purification leads to similar results as when pure protein (i.e., renaturation after purification) was used. Thus, it is clear that, in Musacchio, performing the purification step prior to renaturation does not lead to any improvement, whereas by contrast, the presently claimed process which interposes a RPC step between solubilization and renaturation leads to an improvement in achieving high yield and high purity of recombinant chemokines.

As Proudfoot is only applied by the examiner for its teaching of a chemokine mutant of SEQ ID NO:1 expressed in *E. coli*, one of ordinary skill in the art would certainly not be motivated to apply Musacchio's process, directed to an OPC protein for which other purification processes are unsuccessful,

to purify a chemokine as disclosed in Li (and Proudfoot), especially since Li instead teaches using a refolding step prior to purification of a recombinant chemokine. Even if one were to interpose a RPC step between solubilization and refolding (as in Musacchio) for purifying a chemokine, which applicants emphatically deny any motivation to do so, there is no expectation however that this interposition of a RPC step would lead to any improvement in yield and purity.

As for the part of the examiner's statement regarding a "common purpose", applicants submit that Musacchio, Li and Proudfoot do not share any "common known purpose". The purpose of Musacchio is to obtain a recombinant Opc protein capable of being correctly refolded *in vitro*, with a conformation suitable enough to generate functional antibodies (see abstract). In this reference, the purification process from inclusion bodies is adapted for this specific purpose. The purification via RPC was used solely because it was the only purification method that allowed for the recovery of correctly refolded Opc proteins. On the other hand, the purpose of Proudfoot is to provide alternative mutant chemokines effective in the treatment of multiple sclerosis and/or other demyelinated diseases. A method of producing and purifying such alternative mutants is disclosed notably in Examples 1b-c. There is no suggestion whatsoever for

the use of RPC for the purification of chemokines. The purpose in Li is also different. It is to provide alternative methods of purification of recombinant proteins, such as chemokines, expressed as inclusion bodies. Preferably, such methods improve the yield and purity of recombinant proteins from cell lysates. However, it is clear from the reference that the process has to be performed in the specific order of: 1) solubilization, 2) refolding, 3) purification.

Accordingly, Musacchio, Li and Proudfoot cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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